Use of the Xpert MTB/RIF assay in the diagnosis of tuberculous meningitis: A cautionary note

To the Editor: The Xpert MTB/RIF (Cepheid) assay is a nucleic acid amplification test developed to detect mycobacterial tuberculosis (MTB) infection and rifampicin resistance. It is a closed system, requires minimal training to use, and produces a result in a few hours. When used as an initial diagnostic test replacing smear microscopy for pulmonary tuberculosis, the Xpert MTB/RIF has a pooled sensitivity of 88%.[1] The application of this test has been extended to extrapulmonary samples, including cerebrospinal fluid (CSF).

The World Health Organization (WHO) evaluated the results of 709 CSF samples tested with Xpert MTB/RIF in 16 studies using culture as a reference standard. Sensitivity varied widely, ranging from 51% to 100%.[1] Using a 3 ml volume of CSF and including a concentration step increased sensitivity.[1,2] The WHO recommends that the Xpert MTB/RIF should be the first test to be undertaken on CSF from patients with suspected tuberculous meningitis (TBM). However, caution is advised, as the following case illustrates.

A 43-year-old HIV-positive man was admitted to a peripheral hospital in South Africa with a 2-week history of headache and a more recent onset of slurred speech, inability to walk and impaired consciousness. A computed tomography scan of the brain showed mild hydrocephalus and basal enhancement. Lumbar puncture revealed an opening pressure of 4 cm H_2O, yellow colour, lymphocytes 300/l, a protein level of 1.06 g/l and glucose level of 1.3 mmol/l. The Xpert MTB/RIF was negative. On the basis of this negative test result, initiation of antituberculosis (anti-TB) therapy was deferred and ceftriaxone was started. The patient was referred to the neurology unit at Inkosi Albert Luthuli Central Hospital in Durban 4 days later. He was noted to have a Glagow Coma Score of 8/15, meningism and normal optic fundi. He could move all his limbs. Anti-TB drugs and steroids were commenced, but he died within 3 hours of admission.

Ignoring the Xpert MTB/RIF result, this patient's clinical, radiological and CSF profile is consistent with probable TBM.[3] As standard of care, he would have been started on anti-TB therapy and steroids while awaiting the other laboratory results. The WHO, understandably, based its recommendation on studies done in research settings, where as much as 3 ml of CSF was used in at least one study.[2] For busy routine laboratories the extra step of concentration may be burdensome, and moreover they are unlikely to receive such a large volume of CSF.

As this test for TBM becomes more widely available it will be requested at all levels of care by medical personnel who have varying degrees of clinical skill, knowledge and experience. Herein lies the concern. Clinicians need to understand that, as with other tests for diagnosis of TBM, the Xpert MTB/RIF is a good 'rule-in' test (i.e. specificity approaching 100%) but a poor 'rule-out' test (moderate sensitivity).[4] A negative test does not exclude TBM. Clinical judgement is required. Any delay in initiating therapy risks an unacceptable outcome for the patient.

The Xpert MTB/RIF test should be subjected to post-WHO recommendation scrutiny to determine how well it performs in routine clinical practice for the diagnosis of TBM.

Ahmed I Bhigjee

Department of Neurology, Nelson R Mandela School of Medicine, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

bhigjee@ukzn.ac.za

1. WHO policy update. Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children. http://apps.who.int/iris/bitstream/10665/112472/1/9789241506335_eng.pdf (accessed 21 July 2014).
2. Patel VB, Theron G, Lenders L, et al. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculosis meningitis in a high burden setting: A prospective study. PLoS Med 2013;10(10):e1001536. [http://dx.doi.org/10.1371/journal.pmed.1001536]
3. Marais S, Thwaites G, Schoeman JF, et al. Tuberculous meningitis: A uniform case definition for use in clinical research. Lancet Infect Dis 2010;10(11):803-812. [http://dx.doi.org/10.1016/S1473-3099(10)70138-9]
4. Solomons RS, van Elsland SL, Visser DH, et al. Commercial nucleic acid amplification tests in tuberculous meningitis – a meta-analysis. Diag Microbiol Infect Dis 2014;78(4):398-403. [http://dx.doi.org/10.1016/j.diagmicrobio.2014.01.002]

S Afr Med J 2014;104(10):650. DOI:10.7196/SAMJ.8735